Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
P04-094PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/009398	25.06.2004	26.06.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant		
TAISHO PHARMACEUTICAL CO., LTD.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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International application No.
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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 6, 8, 10-15, 17-57	YES
	Claims	1-4, 7, 9, 16, 58, 59	NO
Inventive step (IS)	Claims		YES
	Claims	1-59	NO
Industrial applicability (IA)	Claims	1-59	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: JP 2000-86597 A (F. Hoffmann-La Roche AG.), 28 March 2000, claims and examples 28, 30 and 31

Document 2: WO 02/68380 A1 (Eli Lilly and Co.), 06 September 2002, claims

Document 3: JP 2001-525825 A (Eli Lilly and Co.), 11 December 2001, claims

Document 4: JP 2000-500754 A (Eli Lilly and Co.), 25 January 2000, claims

Document 5: JP 2000-336071 A (Taisho Pharmaceutical Co., Ltd.), 05 December 2000, claims and paragraphs [0004] and [0104]

Document 6: WO 02/605 A1 (Taisho Pharmaceutical Co., Ltd.), 03 January 2002, claims

(1)

The inventions set forth in claims 1 to 4, 7, 9, 16, 58 and 59 lack novelty and do not involve an inventive step in the light of document 1 cited in the international search report.

Document 1 discloses 2-amino-3-methoxy-bicylo [3.1.0] hexane-2,6-dicarboxylic acids; 3-allyloxy-2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acids; 3-

allyloxy-2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl esters; 2-amino-3-benzyloxy-bicyclo [3.1.0] hexane-2,6-dicarboxylic acids; and 2-amino-3-benzyloxy-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl esters. Therein, document 1 further indicates that said compounds are useful as agents for regulating the functions of group II metabotropic glutamate receptors.

In addition, the compounds in question are included within the scope of the group of compounds that are set forth in claims 1 to 4, 7, 9, 16, 58 and 59; therefore, the effects that are ascribed to the inventions set forth in the present application by the applicant in the written response have no affect upon the findings in relation to the novelty or the inventive step of the inventions in question.

(2)

The invention set forth in claims 5, 6, 8, 10, 22, 23, 34, 46, 50, 52, 54 and 56 does not involve an inventive step in the light of document 1 cited in the international search report.

Refer to the explanation in section (1), above.

Furthermore, in the light of the disclosures in paragraphs [0006] to [0008] and [0089] it is possible to infer that the regulating activity is imparted by the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid skeleton of the compounds in question; therefore, it would not require significant creativity for a person skilled in the art to conceive of attempting to change the substituent groups that bond to the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acids, as appropriate, in

order to obtain compounds that exhibit a heightened activity.

In the written response, the applicant asserts that the compounds set forth in the present application exhibit an advantageous effect based on the fact that document 1 does not present measurements of the inhibitory activities of the compounds that are disclosed therein and does not make any direct or indirect disclosure in relation to the fact that the oral administration of a diester will increase the internal exposure dose of the dicarboxylic acid. However, the examples from the description of the present application do not clearly demonstrate that the compounds from the inventions set forth in the present application have a heightened inhibitory action in comparison to the compounds that are disclosed in document 1, and do not clearly demonstrate that the oral administration of a diester will increase the internal exposure dose of the dicarboxylic acid. As a result, said assertions by the applicant have no affect upon the findings in relation to the inventive step of the inventions in question.

(3)

The inventions set forth in claims 1 to 59 do not involve an inventive step in the light of documents 1 to 6 cited in the international search report.

Refer to the explanations in section (1) and (2), above.

The compounds that are set forth in the present application differ from the compounds that are disclosed in document 1 in that it is possible for the substituent group in position 3 to have groups with various

structures in addition to the alkoxy groups.

Meanwhile, documents 2 to 5 disclose 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives which have the same activity and the same skeleton as the derivatives that are disclosed in document 1, and the substituent groups that are capable of bonding to position 4 of the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acids in said derivatives include groups with the same structure as the Y group in formulas [I] and [II] set forth in the present application. In addition, the substituent groups in position 4 of the compounds that are disclosed in documents 2 and 5 include the same alkoxy groups as the substituent groups in position 3 of the compounds that are disclosed in document 1; therefore, it would have been easy to predict that it is possible to maintain the activity of the substituent group in position 4 of a bicyclo [3.1.0] hexane even if said group were to be substituted into position 3 thereof. In other words, it would have been easy for a person skilled in the art to conceive of attempting to substitute the substituent groups in position 3 of the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives that are disclosed in document 1 with substituent groups that have the same structures as the substituent groups in position 4 of the compounds that are disclosed in documents 2 to 5, which have the same skeleton and exhibit the same activity.

In addition, document 5 indicates that bonding fluorine to position 6 of the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives will affect the metabolic stability and the pharmacological actions thereof. Furthermore, the compounds that are disclosed in

document 5 have the same activity and the same skeleton as the derivatives that are disclosed in document 1, as is indicated above; therefore, it would have been possible to predict that the substituent groups therein will also impart similar effects. As a result, it would have been easy for a person skilled in the art to conceive of attempting to bond fluorine to position 6 of the compounds that are disclosed in document 1 in order to obtain compounds that exhibit a heightened activity.

Furthermore, document 6 also discloses 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives that have the same activity and the same skeleton as the derivatives that are disclosed in document 1. Therein, document 6 presents various structures for the alcohol that forms the carboxyl group and the ester in said derivatives; therefore, it would have been easy for a person skilled in the art to conceive of esterifying the carboxyl groups of the compounds that are disclosed in document 1 like in the compounds that are disclosed in document 6.

In addition, the examples from the description of the present application do not clearly demonstrate that the compounds from the inventions set forth in the present application have a heightened inhibitory action in comparison to the compounds that are disclosed in document 6, and do not clearly demonstrate that the oral administration of a diester will increase the internal exposure dose of the dicarboxylic acid. As a result, said assertions by the applicant have no affect upon the findings in relation to the inventive step of the inventions in question.

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Box No. VI **Certain documents cited**

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 03/61698 A1 [E,X] [E,Y]	31.07.2003	26.12.2002	27.12.2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)